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QUEEN Thomas	Queen Thomas
Printed Name	Signature

REISSUE PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of)
U.S. Patent No. 6,008,216)
)
Applicants: Chakrabarti, et al.)
)
Application No.: Unassigned)
)
Filed: December 18, 2001)
)
For: PROCESS FOR PREPARING 2-METHYL- THIENO-BENZODIAZEPINE)
)
Docket No.: G-1265I)

PRELIMINARY AMENDMENT PURSUANT TO 37 C.F.R. § 1.173(b)(2)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a preliminary amendment accompanying an application for reissue of United States Letters Patent No. 6,008,216, to Jiban Kumar Chakrabarti, Terrence Michael Hotten, and David Edward Tupper, and assigned of record to Eli Lilly and Company. Prior to examination of the above-identified application, entry of the following preliminary amendments is respectfully requested.

AMENDMENTS

IN THE CLAIMS:

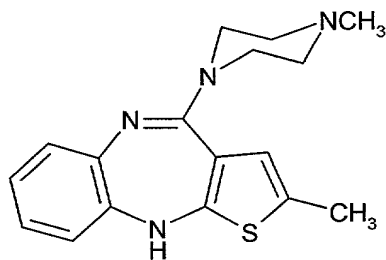
Please amend claim 1 as follows:

1. (once amended) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

- A) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, [propionaldehyde] propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- B) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with a slurry of sodium hydride dispersed in oil in tetrahydrofuran and [2-fluoro-nitrobenzene] 2-fluoronitrobenzene;
- C) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- D) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.

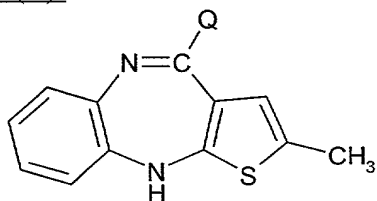
Please add the following new claims 2-26.

2. (new) A process for producing a compound of formula (I):



formula (I)

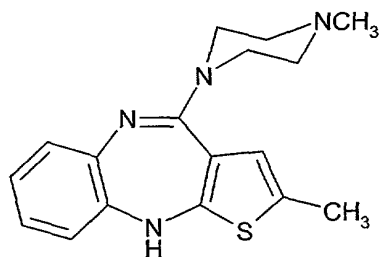
or an acid addition salt thereof, which comprises reacting N-methylpiperazine with a compound of formula (II):



formula (II)

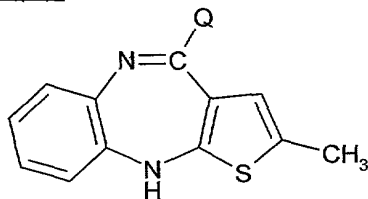
in which Q is an amino group; a mono- or dialkyl-substituted amino group, wherein each alkyl substituent contains 1 to 4 carbon atoms; hydroxyl; thiol; alkoxy; alkylthio; alkylsulphonyl group containing 1 to 4 carbon atoms; or a halogen atom.

3. (new) A process for producing a compound of formula (I):



formula (I)

or an acid addition salt thereof, which comprises reacting N-methylpiperazine with a compound of formula (II):



formula (II)

wherein Q is NH₂, or a salt thereof; hydroxyl; or thiol.

4. (new) The process according to claim 3 wherein Q is NH₂ or a salt thereof.

5. (new) The process according to claim 4 wherein Q is NH₂.

6. (new) The process according to claim 4 wherein Q is the NH₂ salt form.

7. (new) The process according to claim 6 wherein the NH₂ salt form is the hydrochloride salt.

8. (new) The process according to claim 3 wherein the process is carried out at a temperature of from 50°C to 200°C.

9. (new) The process according to claim 7 wherein the process is carried out at a temperature of from 50°C to 200°C.

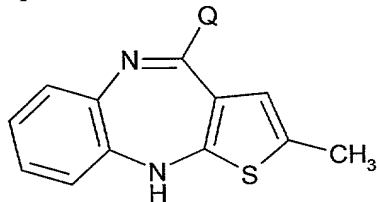
10. (new) The process according to claim 5 wherein the process is carried out at a temperature of from 50°C to 200°C.

11. (new) The process according to claim 7 wherein the process is carried out at a temperature of 100°C to 150°C.

12. (new) The process according to claim 3 wherein Q is hydroxyl.

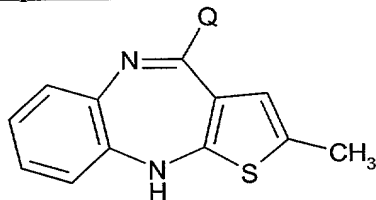
13. (new) The process according to claim 3 wherein Q is thiol.

14. (new) A compound of the formula:



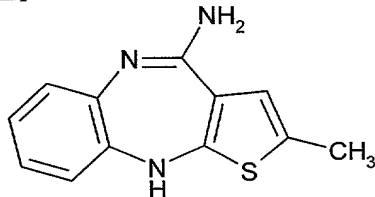
wherein Q is an amino group; a mono- or dialkyl-substituted amino group, wherein each alkyl substituent contains 1 to 4 carbon atoms; hydroxyl; thiol; alkoxy; alkylthio; alkylsulphonyl group containing 1 to 4 carbon atoms; or a halogen atom.

15. (new) A compound of the formula:



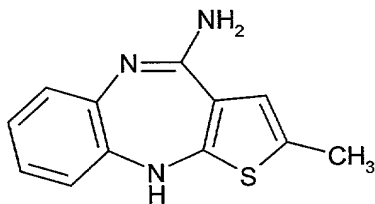
wherein Q is NH₂, or a salt thereof; hydroxyl; or thiol.

16. (new) A compound of the formula:

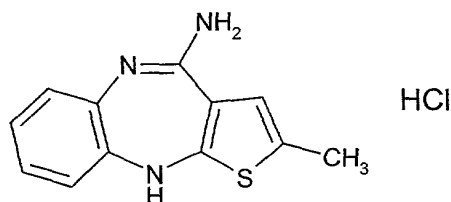


or a salt thereof.

17. (new) A compound of the formula:



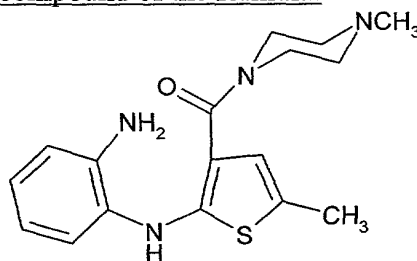
18. (new) A compound of the formula:



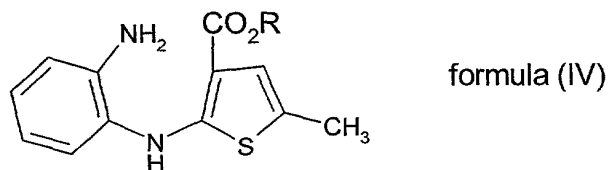
19. (new) A compound according to claim 15 wherein Q is hydroxyl.

20. (new) A compound according to claim 15 wherein Q is thiol.

21. (new) A compound of the formula:



22. (new) A compound of the formula:



in which R is an ester group.

23. (new) A compound according to claim 22 wherein R is C₁₋₄ alkyl.

24. (new) A compound according to claim 22 wherein R is methyl.

25. (new) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

- A) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- B) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with potassium carbonate or lithium hydroxide in dimethylsulphoxide and 2-fluoronitrobenzene;

- C) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- D) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.

26. (new) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

- A) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- B) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with aqueous sodium hydroxide in dimethylsulphoxide and 2-fluoronitrobenze;
- C) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- D) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.

REMARKS

Attached herewith, pursuant to 37 C.F.R. § 1.173(c), is a chart, at Appendix A, providing the status of all patent claims and of all added claims. Further included in the chart, pursuant to 37 C.F.R. § 1.173(c), is an indication of the passages in the originally filed application where, at the very least, the claims find support. Claim 1 has been amended to correct a typographical error in step A and a typographical error in step B.

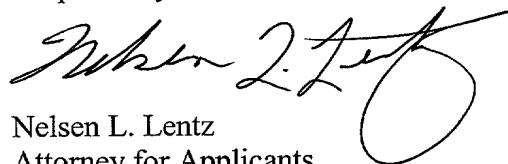
A clean set of all pending claims 1-26, original and newly added, are provided for the convenience of the Examiner at Appendix B. It is respectfully submitted that entry of the amendments submitted herewith introduce no new matter to the reissue application. In addition, it is respectfully submitted that since this reissue application is being filed within

Docket No. G-1265I

two years of the issue date of United States Letter Patent No. 6,008,216, broader claims than those in the issued patent are permissible.

It is respectfully submitted that the reissue application is now in order for allowance.

Respectfully submitted,



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Eli Lilly and Company
Patent Division/NLL
Lilly Corporate Center
Indianapolis, Indiana 46285

December 18, 2001

APPENDIX A –**STATUS OF CLAIMS AND SUPPORT FOR CLAIM CHANGES PURSUANT TO
37 C.F.R. § 1.173(c)**

<u>Claim</u>	<u>Status</u>	<u>Indication of Support in the Disclosure</u>
1	pending	Column 9, lines 22-35, column 14, lines 7 to 67 and column 15, lines 1 to 24 at Example 1, describes the process.
2	pending	Column 8, lines 24-39 and lines 56-61 describe the process.
3	pending	Column 8, lines 24-39 and lines 62-63, and column 9, lines 16-18 describe the process.
4	pending	Column 8, line 63 describe amino as most preferred and column 9, lines 16-18 describe that when Q is NH ₂ the amidine can be in a salt form.
5	pending	Column 8, line 63 describes that amino is most preferred..
6	pending	Column 9, lines 16-17 describe that when Q is NH ₂ the amidine can be in a salt form.
7	pending	Column 9, lines 16-18 describe that when Q is NH ₂ the amidine can be in a salt form, for example a salt of a mineral acid such as the hydrochloride.
8	pending	Column 8, lines 64-65 describe a reaction temperature range of the process.
9	pending	Column 8, lines 64-65 describe a reaction temperature range of the process.
10	pending	Column 8, lines 64-65 describe a reaction temperature range of the process.
11	pending	Column 9, lines 20-21 describe a temperature range of the process.
12	pending	Column 8, lines 62-63 describe that Q can be hydroxyl.
13	pending	Column 8, lines 62-63 describe that Q can be thiol.
14	pending	Column 8, lines 30-38 and column 10, lines 41-42 describe the intermediate compounds.
15	pending	Column 10, lines 41-45 describe the intermediate compounds.
16	pending	Column 8, line 63, column 9, lines 16-18, and column 10, lines 41-45, describe the intermediate compounds.
17	pending	Column 8, lines 62-63 and column 10, lines 41-45 describe the intermediate compound with amino being most preferred..
18	pending	Column 8, line 63, column 9, lines 16-18 and column 10, lines 41-45 describe the intermediate compound.
19	pending	Column 10, lines 41-45 describe the intermediate compounds.

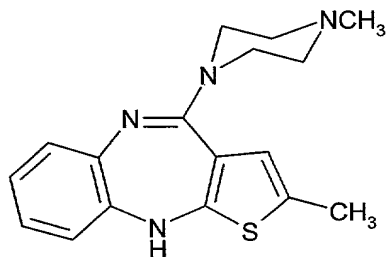
<u>Claim</u>	<u>Status</u>	<u>Indication of Support in the Disclosure</u>
20	pending	Column 10, lines 41-45 describe the intermediate compounds.
21	pending	Column 8, lines 43-53 describe the intermediate compound of formula (III)..
22	pending	Column 10, lines 51-63 describe formula (IV).
23	pending	Column 10, lines 51-63 describe formula (IV) wherein R is C ₁₋₄ alkyl.
24	pending	Column 10, lines 51-63 and column 15, lines 52-63 describe the compound of formula (IV) wherein R is methyl.
25	pending	Column 9, lines 22-34, column 14, lines 7 to 67, and column 15, lines 1 to 24 at Example 1, describe the process.
26	pending	Column 9, lines 22-35, column 14, lines 7 to 67 and column 15, lines 1 to 24 at Example 1, describe the process.

APPENDIX B – CLEAN SET OF ALL PENDING CLAIMS

1. (once amended) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

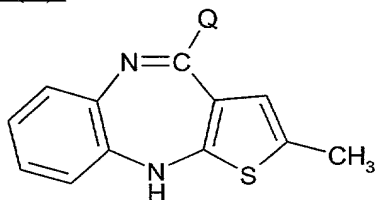
- A) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- B) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with a slurry of sodium hydride dispersed in oil in tetrahydrofuran and 2-fluoronitrobenze;
- C) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- D) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.

2. (new) A process for producing a compound of formula (I):



formula (I)

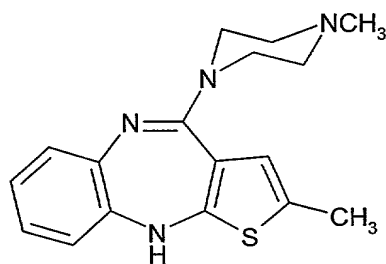
or an acid addition salt thereof, which comprises reacting N-methylpiperazine with a compound of formula (II):



formula (II)

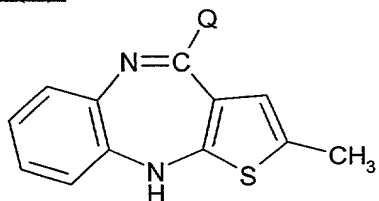
in which Q is an amino group; a mono- or dialkyl-substituted amino group, wherein each alkyl substituent contains 1 to 4 carbon atoms; hydroxyl; thiol; alkoxy; alkylthio; alkylsulphonyl group containing 1 to 4 carbon atoms; or a halogen atom.

3. (new) A process for producing a compound of formula (I):



formula (I)

or an acid addition salt thereof, which comprises reacting N-methylpiperazine with a compound of formula (II):



formula (II)

wherein Q is NH₂, or a salt thereof; hydroxyl; or thiol.

4. (new) The process according to claim 3 wherein Q is NH₂ or a salt thereof.

5. (new) The process according to claim 4 wherein Q is NH₂.

6. (new) The process according to claim 4 wherein Q is the NH₂ salt form.

7. (new) The process according to claim 6 wherein the NH₂ salt form is the hydrochloride salt.

8. (new) The process according to claim 3 wherein the process is carried out at a temperature of from 50°C to 200°C.

9. (new) The process according to claim 7 wherein the process is carried out at a temperature of from 50°C to 200°C.

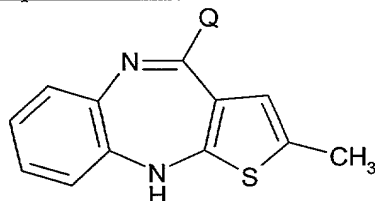
10. (new) The process according to claim 5 wherein the process is carried out at a temperature of from 50°C to 200°C.

11. (new) The process according to claim 7 wherein the process is carried out at a temperature of 100°C to 150°C.

12. (new) The process according to claim 3 wherein Q is hydroxyl.

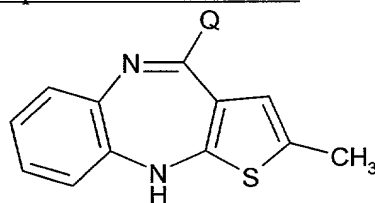
13. (new) The process according to claim 3 wherein Q is thiol.

14. (new) A compound of the formula:



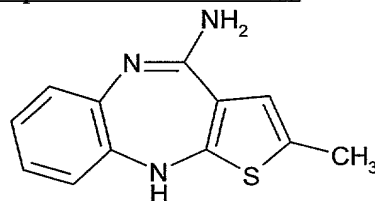
wherein Q is an amino group; a mono- or dialkyl-substituted amino group, wherein each alkyl substituent contains 1 to 4 carbon atoms; hydroxyl; thiol; alkoxy; alkylthio; alkylsulphonyl group containing 1 to 4 carbon atoms; or a halogen atom.

15. (new) A compound of the formula:



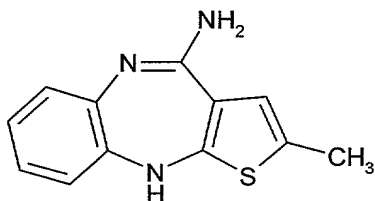
wherein Q is NH₂, or a salt thereof; hydroxyl; or thiol.

16. (new) A compound of the formula:

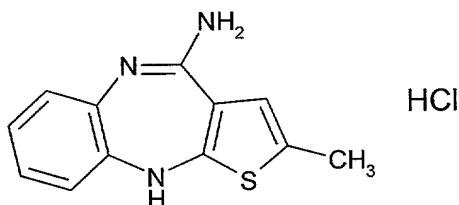


or a salt thereof.

17. (new) A compound of the formula:



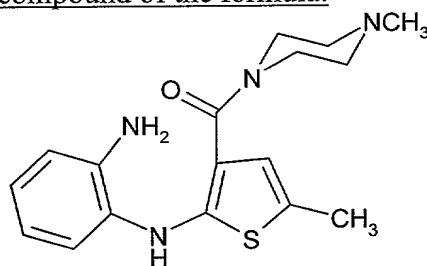
18. (new) A compound of the formula:



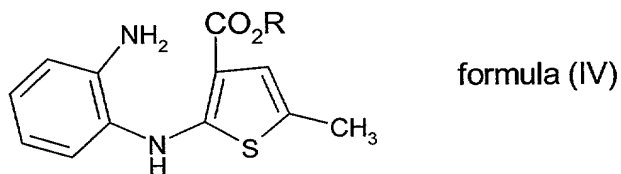
19. (new) A compound according to claim 15 wherein Q is hydroxyl.

20. (new) A compound according to claim 15 wherein Q is thiol.

21. (new) A compound of the formula:



22. (new) A compound of the formula:



in which R is an ester group.

23. (new) A compound according to claim 22 wherein R is C₁₋₄ alkyl.

24. (new) A compound according to claim 22 wherein R is methyl.

25. (new) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

- E) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- F) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with potassium carbonate or lithium hydroxide in dimethylsulphoxide and 2-fluoronitrobenzene;

- G) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- H) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.

26. (new) A method of preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]-benzodiazepine comprising the following steps:

- E) preparing 2-amino-5-methylthiophene-3-carbonitrile by mixing sulfur, propionaldehyde in dimethylformamide, then adding triethyl amine, then adding malononitrile;
- F) preparing 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile from the reaction product of step (A) by reaction with aqueous sodium hydroxide in dimethylsulphoxide and 2-fluoronitrobenze;
- G) preparing 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride from the reaction product of step (B) by reacting with a slurry of 2-(2-nitroanilino)-5-methyl-thiophene-3-carbonitrile in ethanol and a solution of anhydrous stannous chloride in hydrochloric acid;
- H) preparing 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine by refluxing the reaction product of step (C) with a mixture of N-methylpiperazine, dimethylsulphoxide and toluene.